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AAAAATAAAATCAT ATG AAA AAT ATT AAA AAA AAT CAA GAA ATC AAT CTC 66T CGT AAT TCT
K N I K K N Q V M L N S
AAA TTA TTA AAA GAA TAT AAA TCA CAA TCA Q L E N I E Q F E A
K L K E Y S Q L N I E Q F E A
GGT ATT 66T TTA ATT TTA GGA GAT GCT TAT ATT CGT AGT GAT GAA GGT AAA ACT TAT
G I G L I L G D A Y R S R D E G K T Y
TGT ATG CAA TTT CAC TCC AAA AAT AAG GCA TAC ATG GAT CAT GTA TGT TTA TTA TAT GAT
C M Q F E W K N K A Y M D H V C L L Y D
CAA TGG GTA TTA TCA CCT CCT CAT AAA AAA GAA AGA GTT AAT CAT TTA GGT AAT TTA GTA
Q W V L S P H K K E R V N H L G N L V
ATT ACC TGG GGA GCT CAA ACT TTT AAA CAT CAA GCT TTT AAT AAA TTA GCT AAC TTA TTT
I T W G A Q T F K H Q A F N K L A N L F
ATT GTA AAT AAA CTT ATT CCT AAT TTA GAA AAT TAT TTA ACA CCT ATG
I Y N K K L I P N L V E N Y L T P M
AGT CTG GCA TAT TGG TTT ATG GAT GAT GGA GGT AAA TGG GAT TAT AAT AAA AAT TCT CTT
S L A Y W F M D G K W D Y N K N S L
AAT AAA AGT ATT GTA TTA ATT ACA CAA AGT TTT ACT TTT GAA GAA TAT TTA CTT
N K S I V L N T Q F S F T V C Y L V
AAA GGT TTA AGA AAT AAA TTT CAA TTA ATT TGT TAT GTT AAA ATT AAT AAA AAT AAA CCA
K G L R N K F Q L N C Y V K I N K N K P
ATT ATT TAT ATT GAT TCT AGT ATT CTG ATT TTT TAT ATT TTA ATT AAA CCT TAT TTA
I I Y I D S M S Y I F Y N I T K P Y L
ATT CCT CAA ATG ATG TAT AAA CTG CCT AAT ACT ATT TCA TCC GAA ACT TTT TTA AAA TAA
I P Q M Y K L P N T S E T F L K

FIG. I

Bam HI

CCGGATCCATG CAT ATG AAA AAC ATC AAA AAC CAG GTA ATG AAC CTG GGT CGG AAC TCT
 H M K N I K N Q V M N L G P N S
 AAA CTG CTG AAA GAA TAC AAA TCC CAG CTG ATC GAA CTG AAC ATC GAA CAG TTC GAA GCA
 K L K E Y K S Q L I E L N I E Q F E A
 1. GGT ACT GGT CTG ATC CTG GGT GAT GAT GCT TAC ATC CGT TCT CGT GAT GAA GGT AAA ACC TAC
 G L G L I L G D A Y I R S R D E G K T Y
 TGT ATG CAG TTC GAG TGG AAA AAC GCA TAC ATG GAC CAC GTC GAA TGT CTG TAC GAT
 C M Q F E W K N K A Y M D H V C L L Y D
 CAG TGG GTA CTG TCC CCG CAC AAA GAA CGT GTT AAC CAC CTG GGT AAC CTG GTA
 Q W V L S P H K K E R V N H L G N L V
 ATC ACC TGG GGC GCC CAG ACT TTC AAA CAC CAA GCT TTC AAC AAA CTG GCT AAC CTG TTC
 I W G A Q T F K H Q A F N K L A N L F
 ATC GTT AAC AAC AAA ACC ATC CCG AAC AAC CTG GTT GAA AAC TAC CTG ACC CGG ATG
 I V N K A Y K P N I P N I E N Y L T C P M
 2. TCT CTG GCA TAC TGG TTC ATG GAT GAT GGT GGT AAA TGG GAT TAC AAC AAA AAC TCT ACC
 S L A Y W F M D D G G K W D Y N K N S T
 AAC AAA TCG ATC GTA CTG AAC ACC CAG TCT TTC ACT TTC GAA GAA TAC CTG GTT
 N K S I V L N T Q S F T F E V E Y L V
 AAG GGT CTG CGT AAC AAA TTC CAA CTG AAC TGT TAC CTA AAA ATC AAC AAA AAC CGG
 K G L R N K F Q L N C T Y K I N K N K P
 ATC ATC TAC ATC GAT TCT ATG TCT TAC CTG ATC TTC TAC AAC CTG ATC AAA CGG TAC CTG
 I Y I D S M S Y L I F Y N L I K P Y L
 ATC CCG CAG ATG ATG TAC AAA CTG CCG AAC ACT ATC TCC TCC GAA ACT TTC CTG AAA TAA
 I P Q M M Y K L P N T I S S E T F L K
 TAAGTCGACTGAGGATCCGGTAAGTAAGTAA

SalI PstI BamHI

1 and 2: THESE AMINO ACIDS ARE ABSOLUTELY NECESSARY TO PRODUCE CATALYTIC
 ACTIVITY OTHER SUBSTITUTIONS ARE POSSIBLE, SUCH AS DELETIONS
 OF THE 10 FIRST AMINO ACIDS.

FIG. 2

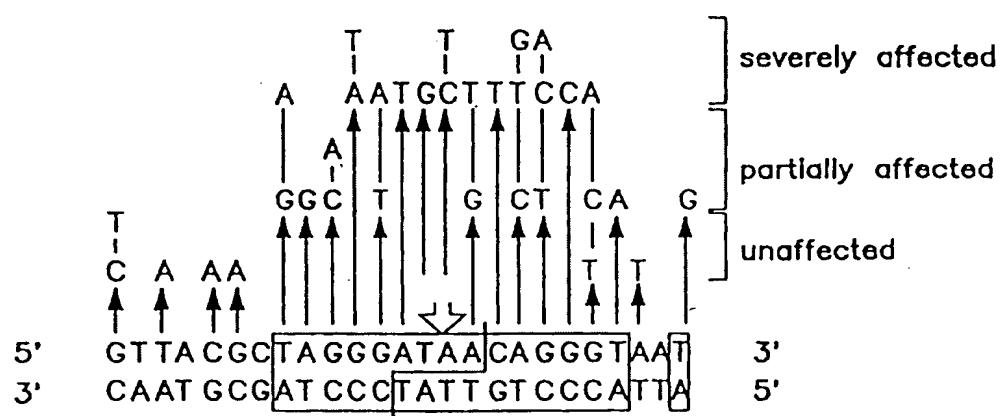


FIG. 3

1667 CGGGACAGGTATCCGGTAAAGGGCAAGGGTGGAACAGGAGGGCACAGGGAGCTTCCAGGGGAAACGGCTGGTATCT 1746
1 1747 TTATAGCCTGCGGGTTTGCACCTCTGAGCTGCGATTTGGTATG CTC AGG GGG GCG GAG 1818
L V R G A E 7
1818 CCT ATG GAA AAA CGC CAG CAA CGC GGC CTT TTT ACG GTT CCT GGC CCT TTG CTG GCC TTT 1878
P E K R Q L F V P L A F 27
1879 TGC TCA CAT GTT CTT TCC TGC GTT ATC CCC TGA TTCTGGATAACCGTATTACCGCTTGGTAGGC 1947
28 C S H V L S C V 1 P 38
1948 TGATACCGCTGCCAGCCGAACGACCGCAGCGAGTCAGTGAGGAGGGAAAGGGAAAGGCCAATACGAAAC 2027
2028 CGCCCTCTCCCCGGCTGGCCGATTACATTA ATG CAG CTG GCA CAG GTT TCC CGA CTG GAA AGC 2094
1 M Q L A R Q V S R L E S 12
2095 GGG CAG TGA GCGAACGCAATTATG TGA GTTAGGCTCACTTAGGGACCCAGGGTTACACTTATG 2164
13 G Q M 1
2165 CTT CCG GCT CGT ATG TTG TGT GGA ATT GTG AGC GGA TAA CAATTTCACACAGGAAACAGCT ATG 2228
2 L P A R M L C G 1 V S G M 1
2229 ACC ATG ATT ACG AAT TCT CAT GTT TGA CAGCTTATCATGATAAGCTTTA ATG CGG TAG TTTATCAC 2295
2 T M 1 P N H V 1
2296 AGTTAAATTGCTAACGCAAGTCAGGGCAACGGTGT ATG AAA TCT AAC AAT GCG CTC ATC ATC CTC GGC 2363
1 M K N A V 1 P V 1 L V 1
2364 ACC GTC ACC CTG GAT GCT GTC GGC ATA GGC TTG GTT ATG CCG GTA CTG CCG GGC CTC TTG 2423
13 T V D A V G L V M P V L P G L L 32
2424 CGG GAT ATC CGC CTG ATG CGT GAA CGT GAC CGA CGT AAC CAC CGC GAC ATG TGT GTG CTG 2483
33 R D 1 R M R E R D G R N H R D M C V L C V L 52
2484 TTC CGC TGG GCA TGC CAG AAC TTC TGG TCC GGT AAC GTG CTG AGC CGC GCC AAG CTT 2543
53 F R W A C Q D N F V S G P A K L S P A K L 72

FIG. 4A

2544	ACT	CCC	CAT	CCC	CCT	GTT	GAC	AAT	TAA	TCATGGCTCGTATA	ATG	TGT	GGAA	ATT	GTC	AGC	GGA	2606
73	T	P	H	P	V	D	N	D	N	BamHI	M	C	G	I	V	S	G	7
2607	TAA	CAATTACACAGGAAACAGGATCC	ATG	CAT	ATG	AAA	AAC	ATC	AAA	AAA	AAC	CAG	GTA	ATG	2670			
8	N	S	K	L	G	H	M	K	N	I	K	N	Q	V	M	12		
2671	AAC	CTG	GGT	GGT	AAAC	TCT	AAA	CTG	CTG	AAA	GAA	TAC	AAA	TCC	CTG	ATC	GAA	2730
13	N	P	N	S	K	E	Y	K	S	Q	L	I	E	L	N	Q	32	
2731	ATC	GAA	CAG	TTC	GAA	GGT	ATC	GGT	CTG	ATC	CTG	GGT	GAT	GCT	TAC	ATC	CGT	2790
33	I	E	Q	F	E	A	G	I	G	L	I	G	D	A	Y	I	R	52
2791	GAT	GAA	GGT	AAA	ACC	TAC	TGT	ATG	CAG	TTC	GAG	TGG	AAA	AAC	AAA	GCA	TAC	2850
53	D	E	G	T	Y	C	M	Q	F	E	W	K	N	K	A	Y	M	72
2851	GTA	TGT	CTG	TAC	GAT	CAG	TGG	GTA	CTG	TCC	CCG	CCG	CAC	AAA	GAA	GGT	GTT	2910
73	V	C	L	Y	D	Q	W	V	S	P	H	P	H	K	K	E	R	92
2911	CAC	CTG	GGT	GTAA	ATC	ACC	TGG	GGC	GCC	GAG	ACT	TTC	AAA	CAC	CAA	GCT	TTC	2970
93	H	N	G	N	V	I	T	W	G	A	Q	T	F	K	H	Q	A	112
2971	AAA	CTG	GCT	AAC	CTG	TTC	ATC	GTT	AAC	AAC	AAA	ACC	ATC	CCG	AAC	AAC	CTG	3030
113	K	L	A	N	L	F	I	V	N	N	K	T	I	P	N	N	L	132
3031	AAC	TAC	CTG	ACC	GGG	ATG	TCT	CTG	6CA	TAC	TGG	TTC	ATG	GAT	GGT	GGT	AAA	3090
133	N	Y	T	P	M	S	T	A	Y	W	F	M	D	G	G	K	W	152
3091	TAC	AAC	AAA	TCT	ACC	AAA	TGG	ATC	GTAA	CTG	ACC	QAC	TCT	TTC	ACT	TTC	GAA	3150
153	Y	N	K	S	T	N	K	G	V	N	T	Q	S	F	T	F	E	172
3151	GAA	GTA	AAA	TAC	CTG	GTT	AAG	GGT	CTG	CGT	AAC	AAA	TTC	CAA	CTG	AAC	TGT	3210
173	E	V	E	Y	L	V	K	G	R	N	K	F	Q	L	N	C	Y	192
3211	ATC	AAC	AAA	AAC	CCG	ATC	TAC	TAC	GAT	TCT	ATG	TCT	TAC	CTG	ATC	TTC	TAC	3270
193	I	N	K	N	K	P	I	Y	I	D	S	M	S	Y	L	I	F	212
3271	CTG	ATC	AAA	CCG	TAC	CTG	ATC	CCG	CAG	ATG	ATG	TAC	AAA	CTG	CG	AAC	ACT	3330
213	L	I	K	P	V	L	P	Q	M	Y	K	M	P	N	T	S	S	232
3331	GAA	ACT	TTC	CTG	AAA	TAA	TAAGTCGACCTGGAGCCCCAAGCTTGGCACTGGCCGCTGTTTACACGTCTGACT	SATT	PSTI								3404	
233	E	T	F	L	K													238

FIG. 4B

	-2	-1	1	M	K	N	I	S	K	K	N	Q	V	10	M	N	L	G	P	N	S
K	L	L		K	E	Y	K	S	Q	L	I	E	L		30	N	I	E	Q	F	E
G	I	G	20	L	I	L	G	D	A	Y	I	R	S		50	R	D	E	G	K	T
C	M	Q	40	F	E	W	K	N	K	A	Y	M	D		70	H	V	C	L	L	Y
Q	W	Y	60	L	S	P	P	H	K	K	E	R	Y		90	N	H	L	G	N	L
I	T	W	80	G	A	Q	T	F	K	H	Q	A	F		110	N	K	L	A	N	L
I	V	N	100	N	K	K	I	I	P	N	N	L	V		130	E	N	Y	L	T	P
G	L	A	120	Y	W	P	M	D	D	G	G	K	W		150	D	Y	N	K	N	S
N	K	S	140	I	V	L	N	T	Q	S	F	T	F		170	E	E	V	E	Y	L
K	G	L	160	R	N	K	F	Q	L	N	C	Y	V		190	K	I	N	K	N	K
I	I	Y	180	I	D	S	M	S	Y	L	I	F	Y		210	N	L	I	K	P	Y
I	P	Q	200	M	M	Y	K	L	P	N	T	I	S		230	S	E	T	F	L	K
			220																		

Positions that can be changed without affecting enzyme activity (demonstrated)
 Positions -1 and -2 are not natural. The two amino acids are added due to cloning strategies

Positions 1 to 10: can be deleted
 Position 36: G is tolerated
 Position 40: M or V are tolerated
 Position 41: S or N are tolerated
 Position 43: A is tolerated
 Position 46: V or N are tolerated
 Position 91: A is tolerated
 Positions 123 and 156: L are tolerated
 Position 223: A and S are tolerated

Changes that affect enzyme activity (demonstrated)

Position 19: L to S
 Position 38: I to S or N
 Position 39: G to D or R
 Position 40: L to Q
 Position 42: T to R
 Position 44: D to E G or H
 Position 45: A to E or D
 Position 46: Y to D
 Position 47: I to R or N
 Position 80: I to S
 Position 144: D to E
 Position 145: D to E
 Position 146: G to E
 Position 147: G to S

FIG. 5

Group I Intron Encoded Endonucleases and Related Endonucleases

	ENDONUCLEASE	RECOGNITION SEQUENCE	CLEAVAGE SITE	▽ INTRON SITE
TWO DODECAPEPTIDE FAMILY (OR 4 BP CUTTERS)	I-Sce I (Saccharomyces mitochondria)	CGC TAGGGATAACAGGGTAATATAGC GCGATCCCTATTGTCCCATATATCG	▽	
	I-Sce IV (Saccharomyces mitochondria)	TTCTCATGATTAGCTCTAATCCATGG AAGAGTACTAATCGAGATTAGGTACC	▽	
	I-Sce II (Saccharomyces mitochondria)	CTT TGGTCACTCCAGAAGTATATATT GAAACCAGTAGGTCTTCATATATAAA	▽	
	I-Ceu I (Chlamydomonas chloroplast)	TAA CGGTCCCTAAGGTAGCGAAATTCA ATT GCCAGGATTCCATCGCTTTAAGT	▽	
	I-Ppo I (Physarum nucleus)	TGACTCTCTAAGGTAGCCAAATGCC ACTGAGAGAAATTCCATCGGTTACGG	▽	
	I-Sce III (Saccharomyces mitochondria)	GGA GGT TTTGGTAACTATTTATTAC CCT CCAAAACCATTGATAAATAATGG	▽	
	I-Cre I (Chlamydomonas chloroplast)	GGGTTCAAAACGTCGTGAGACAGTT CCCAAGTTTGCAGCACTCTGTCAAA	▽	
	Endo. Sce I(RF3) (Saccharomyces mitochondria) (Non intronic)	GAT GCT GTAGGCATAGGCTTGGTTAT CTACGACATCCGTATCCGAACCAATA		
	HO (Saccharomyces nucleus) (Non intronic)	CTT TCCCGCAACAGTATAATTTATAAA GAA AGGCCTTGTCAATTAAAATATT		
	I-Csm I (Chlamydomonas mitochondria) (Putative endonuclease)	ACCATGGGGTCAAATGTCTTCTGGG TGGTACCCCAGTTACAGAAAGACCC	▽	
	I-Pan I (Podospora mitochondria) (Putative endonuclease)	GTGCCTGAATGATAATTATTACCTT CACGGACTTACTATAAATAATGGAAA	▽	
OTHER STRUCTURAL FAMILIES	(Bacteriophage T4)			
	I Tev I	CAACCGCTCAGTAGATGTTTCTTGGGTCTACCGTTAAT GTTGGCAGTCATCTACAAAAGAACCCAGATGGCAAATT	▽	
	I Tev II	CAAGCTTATGAGTATGAAGTGAACACGTATT GTTCGAATACTCATACTTCACTTGTGCAATAA	▽	
	I Tev III	GCTATTCTGTTTATGATCTTTGCGTGTAGCTTTAA CGATAAGCAAAAATACATAGAAAACGCACATCGAAATT	▽	

FIG. 6

EXPRESSION VECTORS

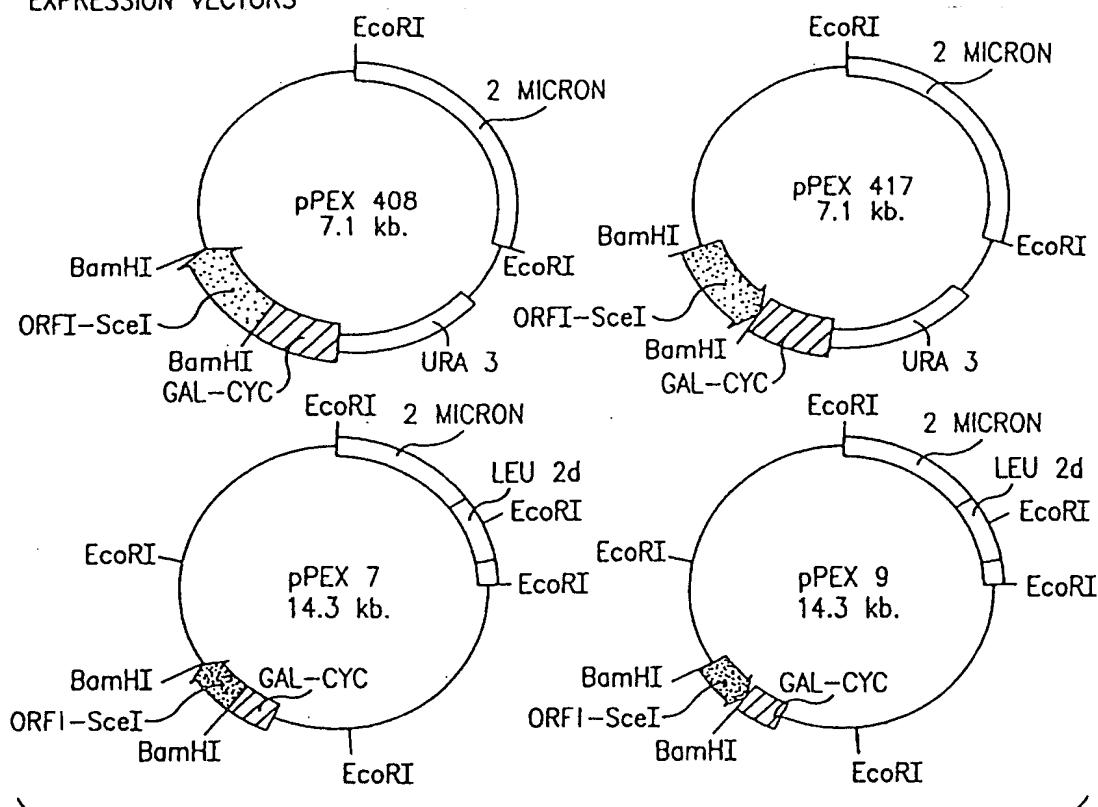


FIG. 7

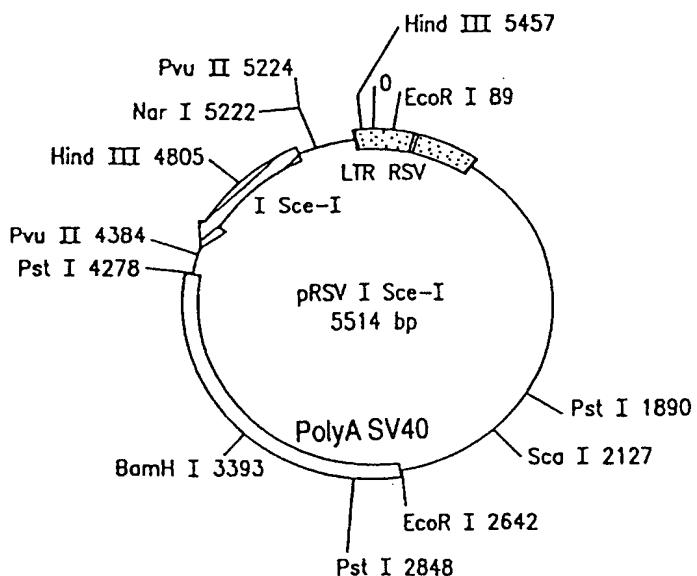


FIG. 8

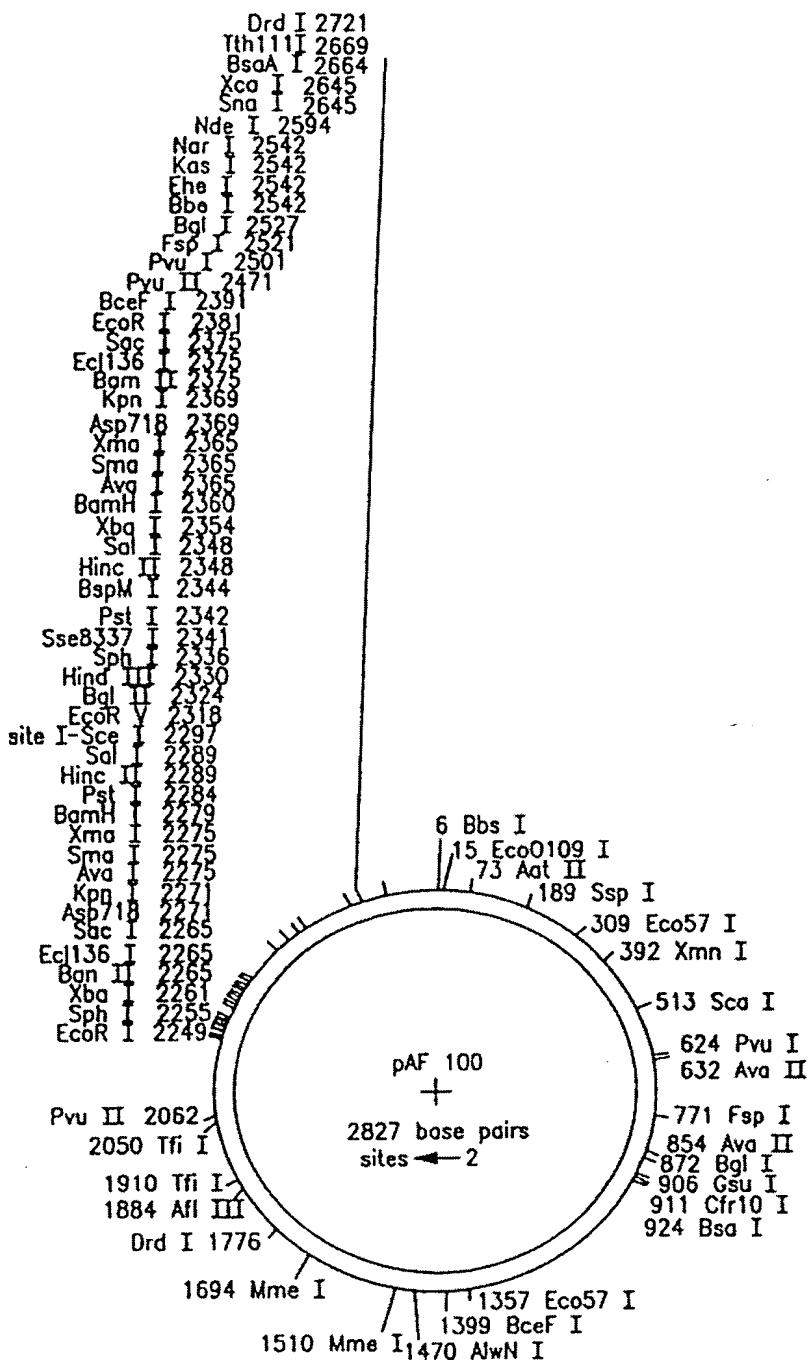
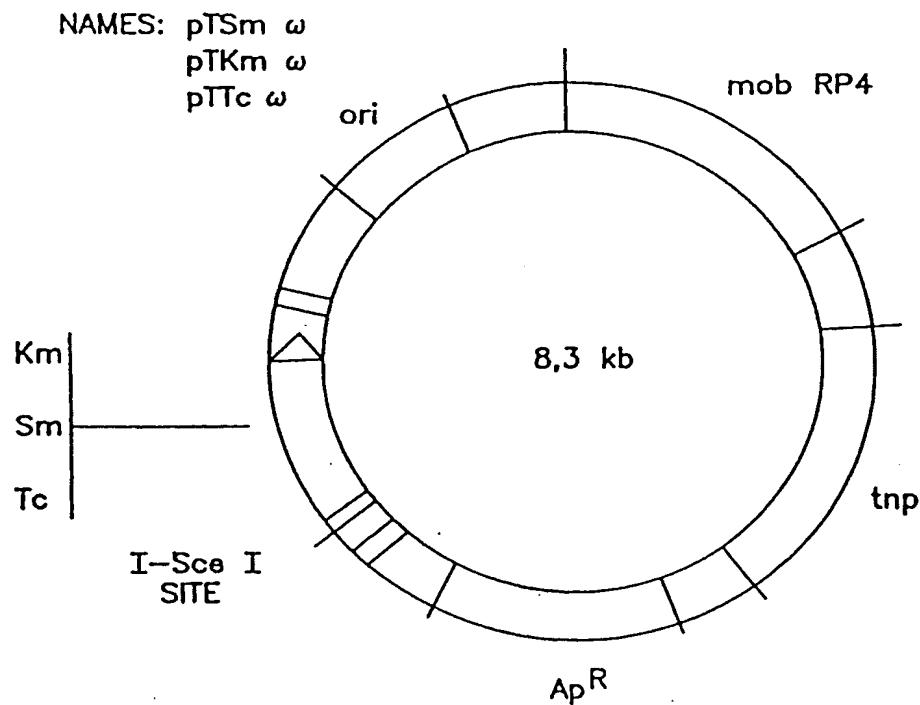


FIG. 9

Sou3A I
Mbo I
Dpn II
ScrF I
Nci I
Msp I
Hpa II
Dsa V
BstK I
Xma I
Sma I
ScrF I
Nci I
Dsa V
Rsa I Dpn I
Nla IV Nla IV
Sac I Csp6 I Alw I
HgiA I BstK I Taq I
Ec1136 I BsoJ I Sal I
Sph I Rma I Kpn I BstY I Hinc II
NspC I Bsp1286 I Bcn I Sfe I
EcoR I Xba I Ban I BamH I Acc I I-Sce I
Apo I Nla III Ban II Bcn I Sfc I Rma I
Toq I Nsp7524 I Alu I Ava I Pst I Hgo I
Alu I Nsp I Bfa I Asp718 Alw I BspW I Bfa I site I-Sce EcoR V
CCAAGCTCGAATT CGCATGCTCTAGAGCTCGGTACCCGGATCCTGCAGTCGACGGT ~~AGGGATAACAGGGTAATACAGAT~~ 2320
GGTTCGAGCTTAAGCGTACGAGATCTGAGCCATGGCCCTAGGACGTCAGCTCGGATCCCTATTGTCCATTATGTCTA
2244 2255 2262 2271 2279 2286 2296 2318
2247 2255 2266 2275 2284 2292
2249 2256 2265 2275 2284 2296
2249 2261 2271 2279 2289 2297
2255 2265 2276 2284
2255 2262 2271 2279 2289
2265 2275 2289
2265 2275 2290
2265 2272 2280
2271 2279
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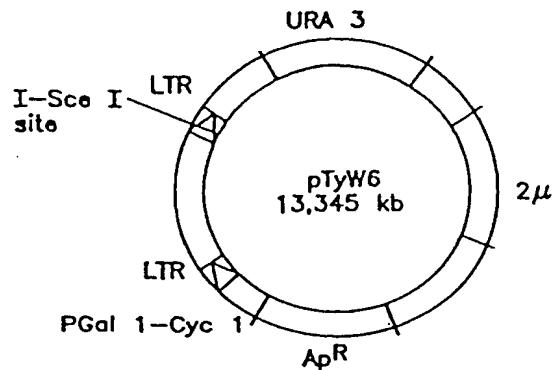
FIG. 10A

FIG. 10B



Construction: pGP 704 from De Lorenzo, with transposase gene and insertion of the linker[I-SceI] in NotI unique site

FIG. 11



Construction: pD 123, from J.D. Boeke
 with insertion of a linker[I-SceI-NotI] in BamHI

FIG. 12

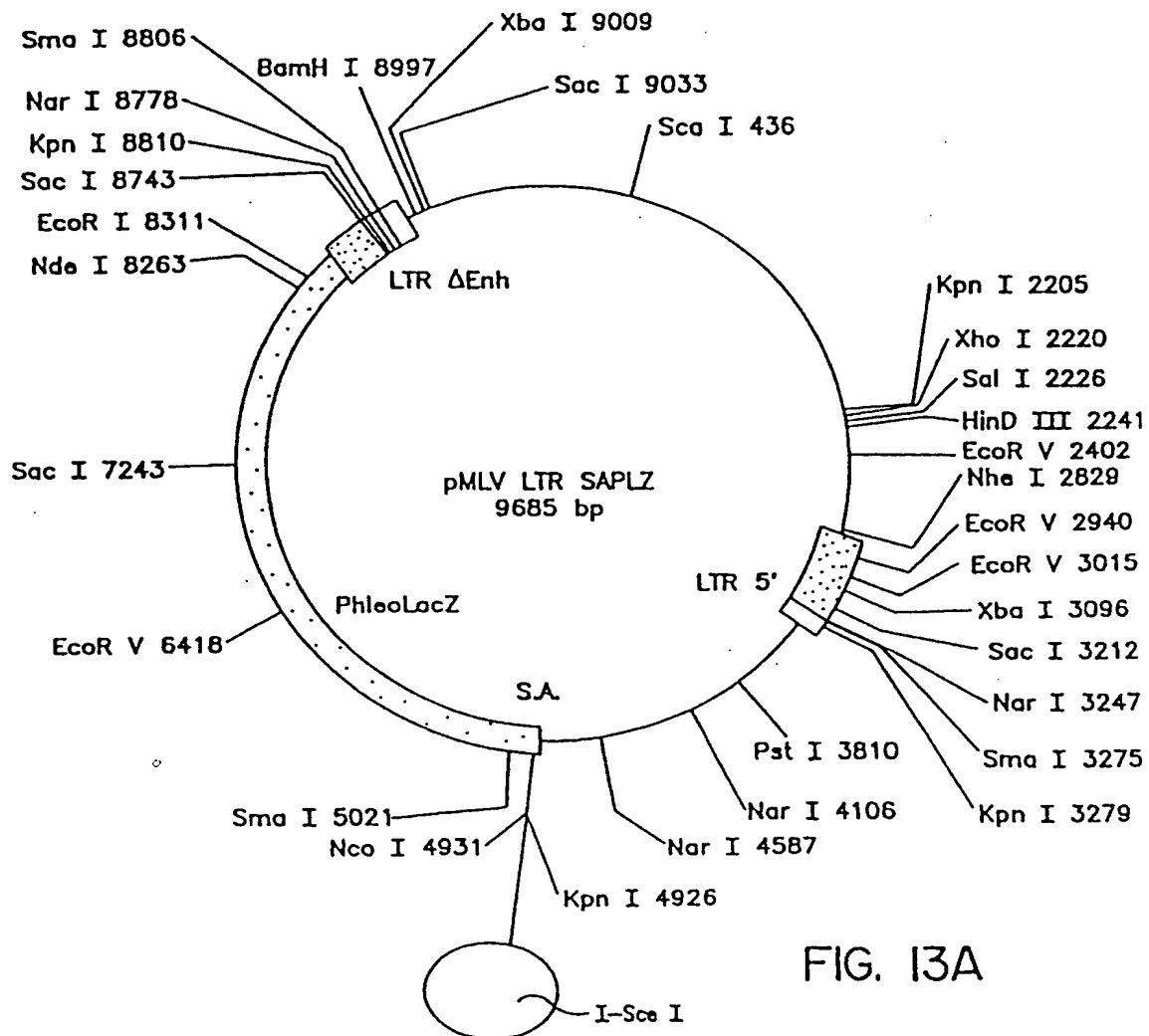


FIG. 13A

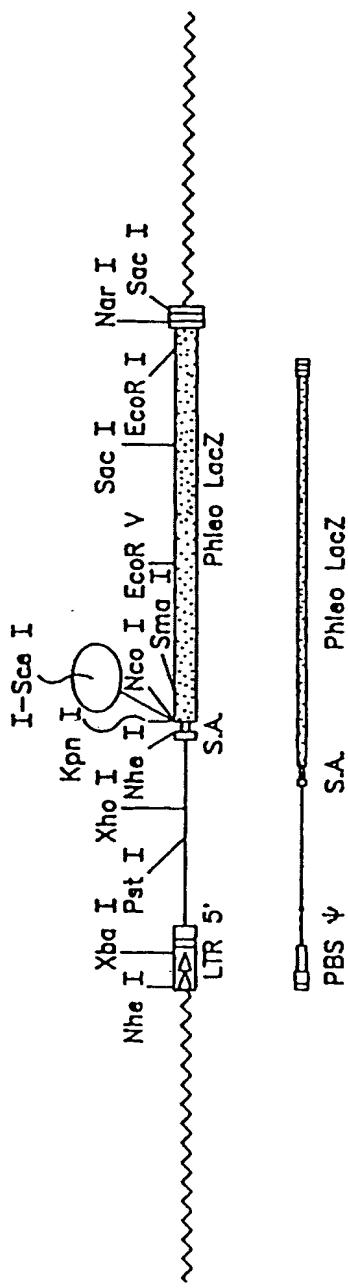


FIG. 13B

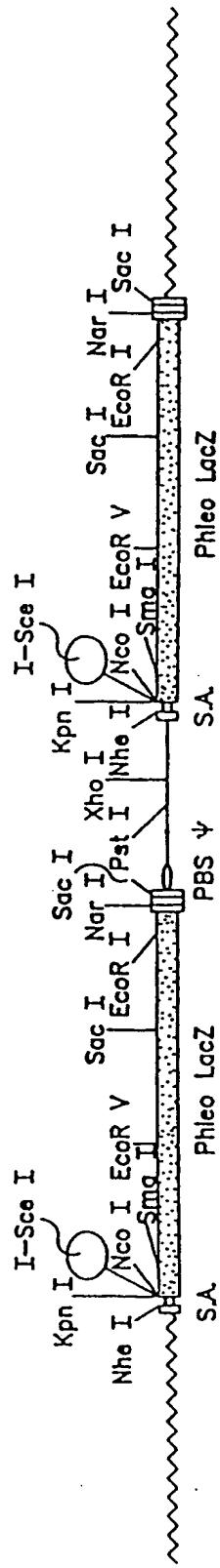


FIG. 13C

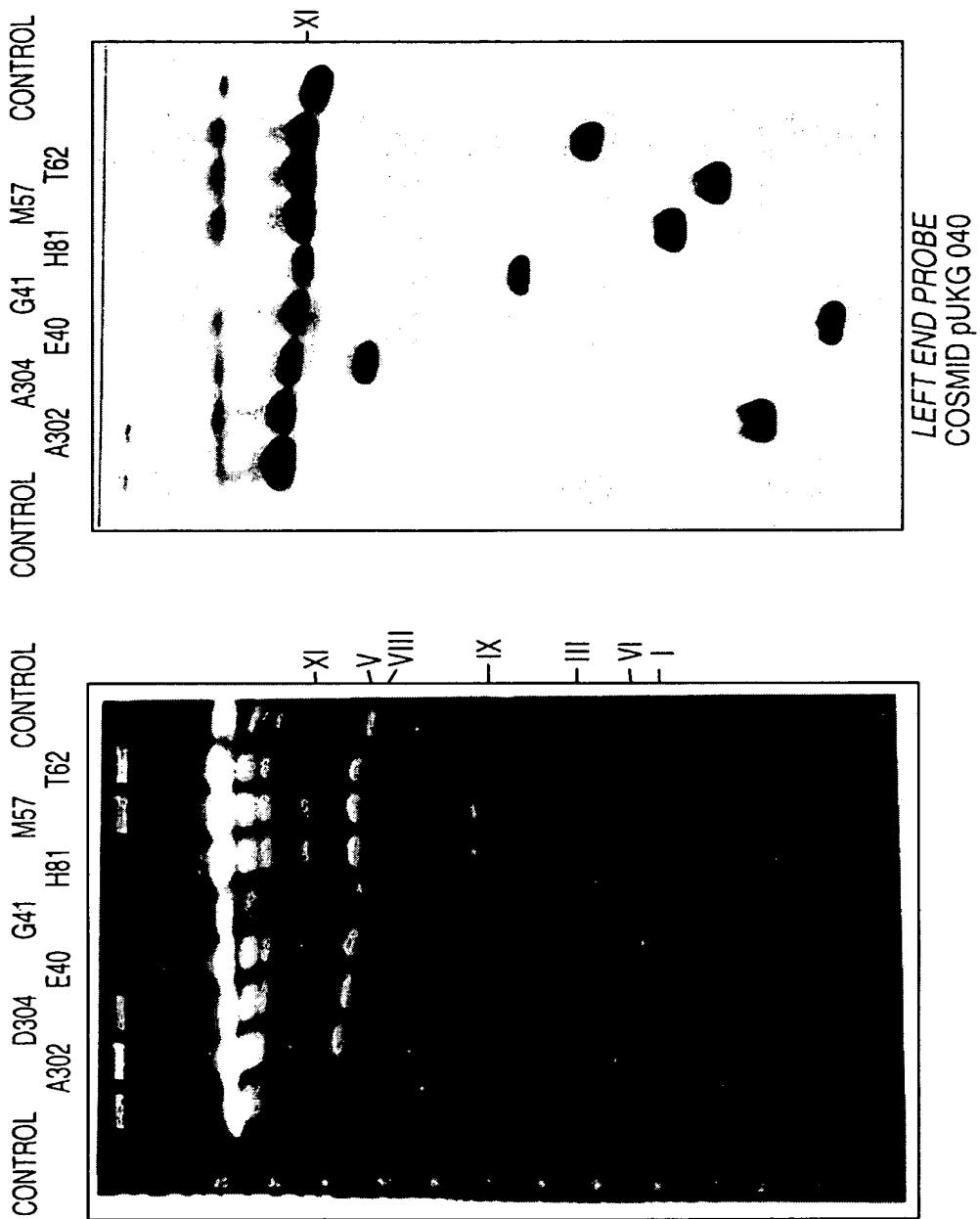


FIG. 14A

FIG. 14B

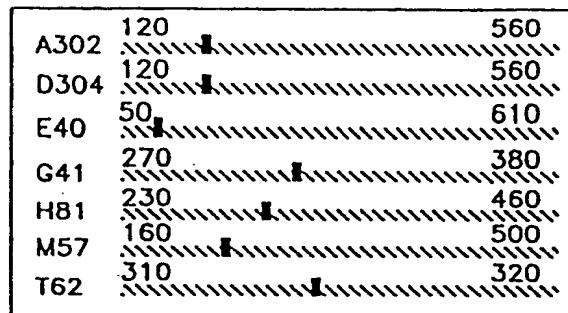


FIG. 15A

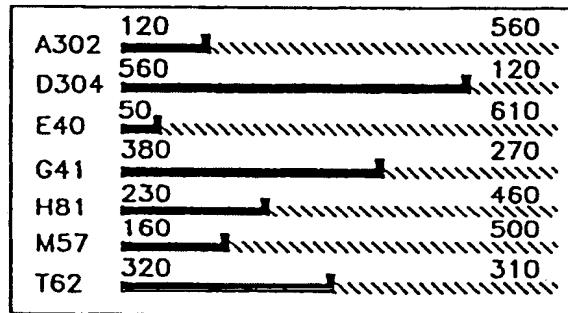


FIG. 15B

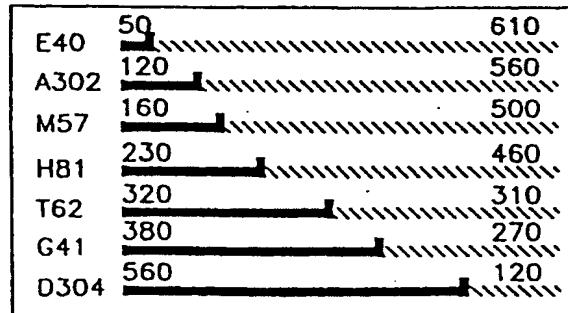


FIG. 15C

FIG. 15D

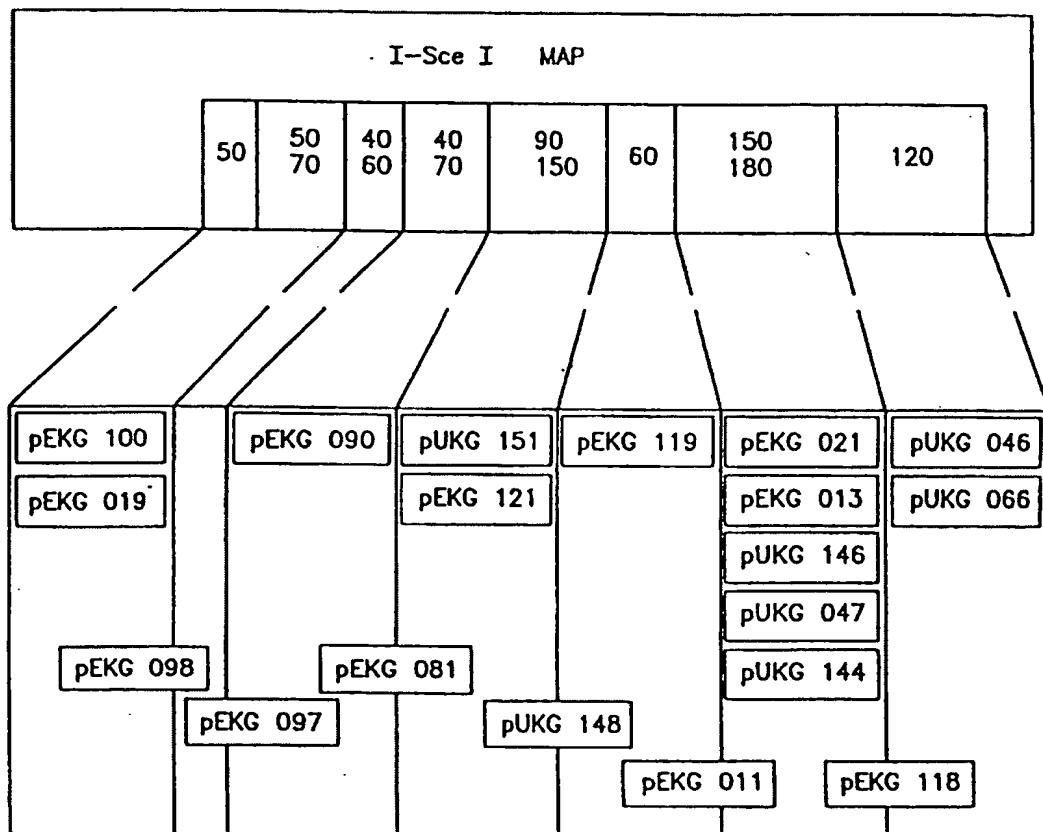


FIG. 15E

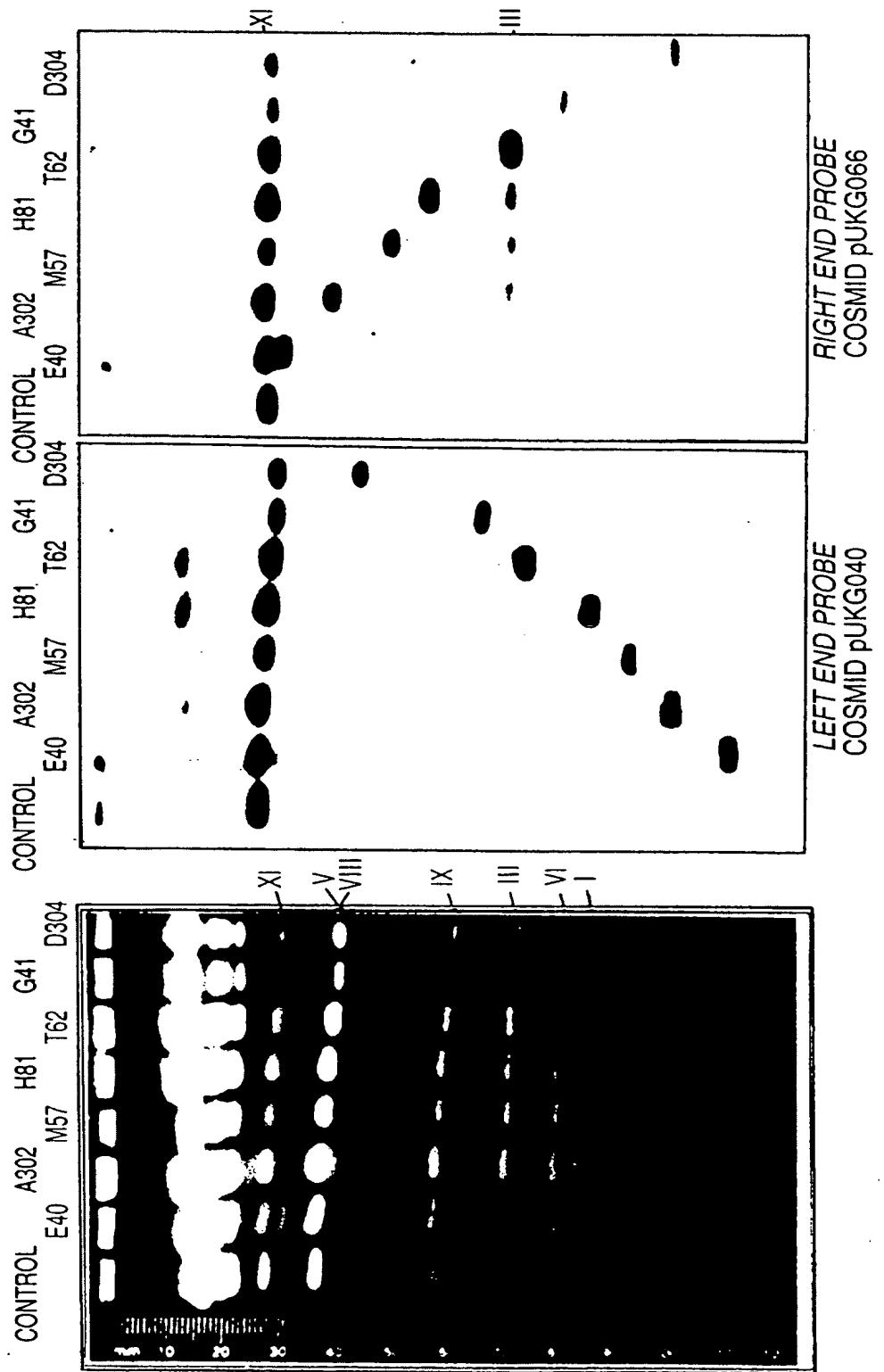


FIG. 16A

FIG. 16B

FIG. 16C

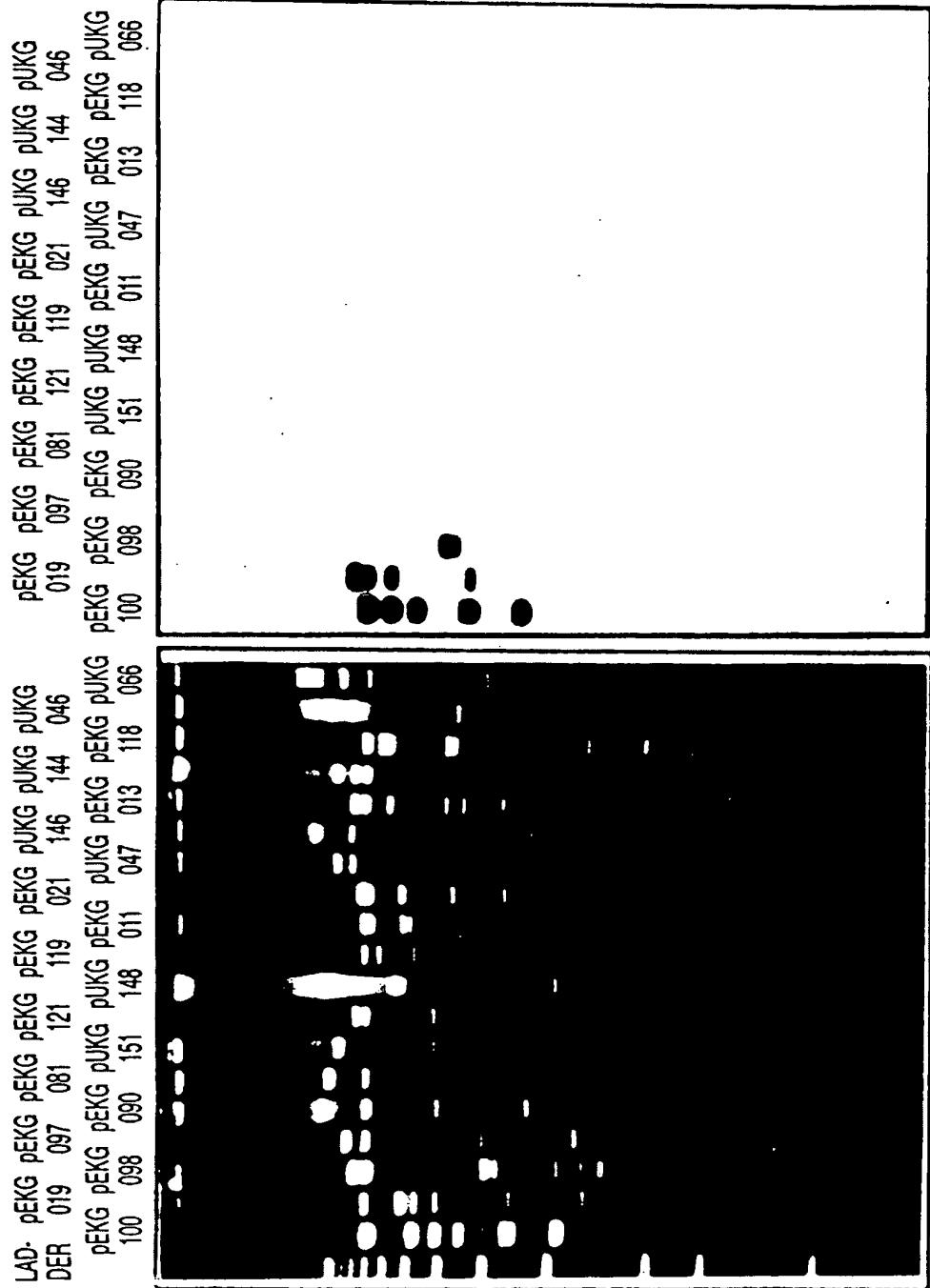


FIG. 17A FIG. 17B

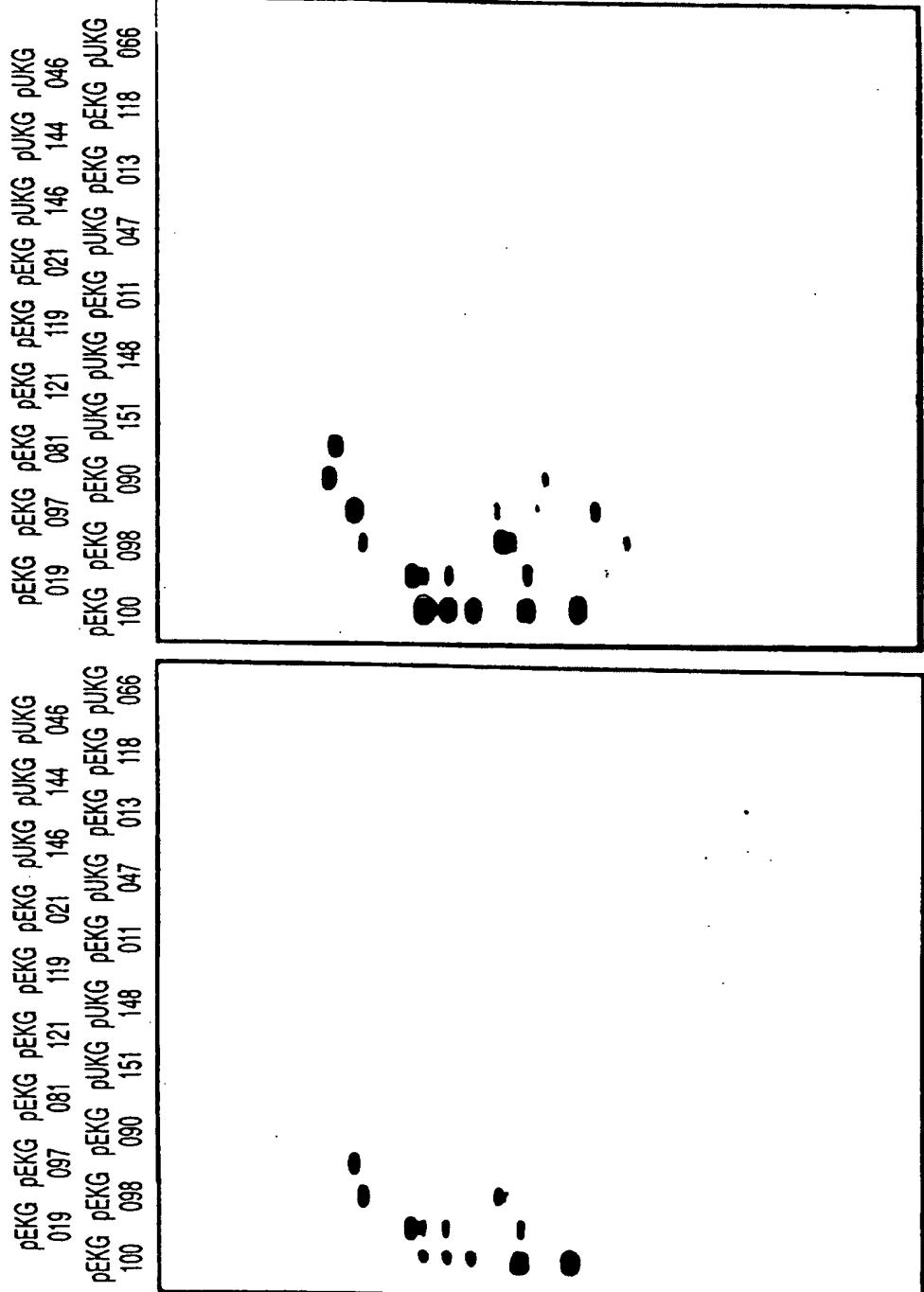


FIG. 17C

FIG. 17D

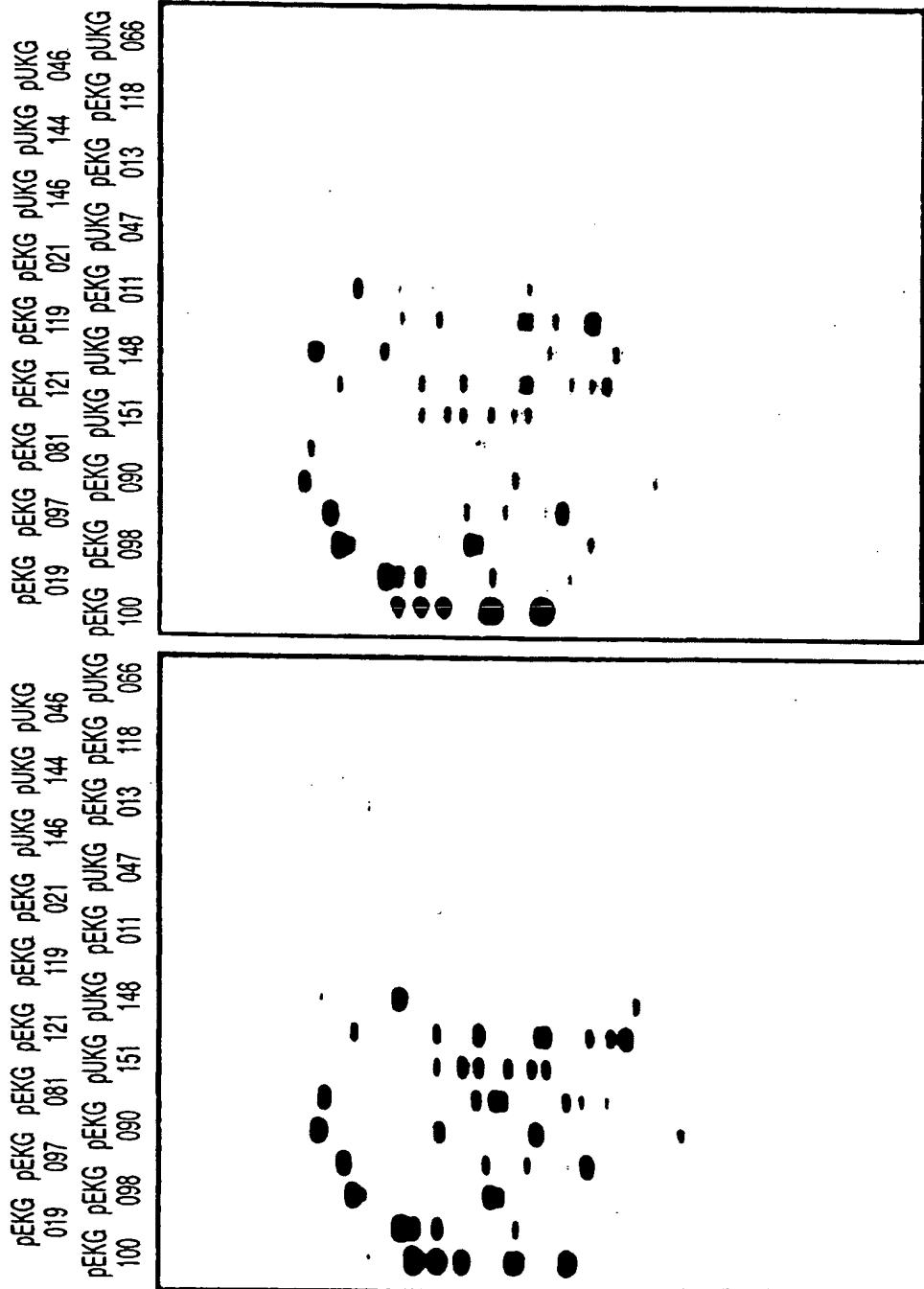
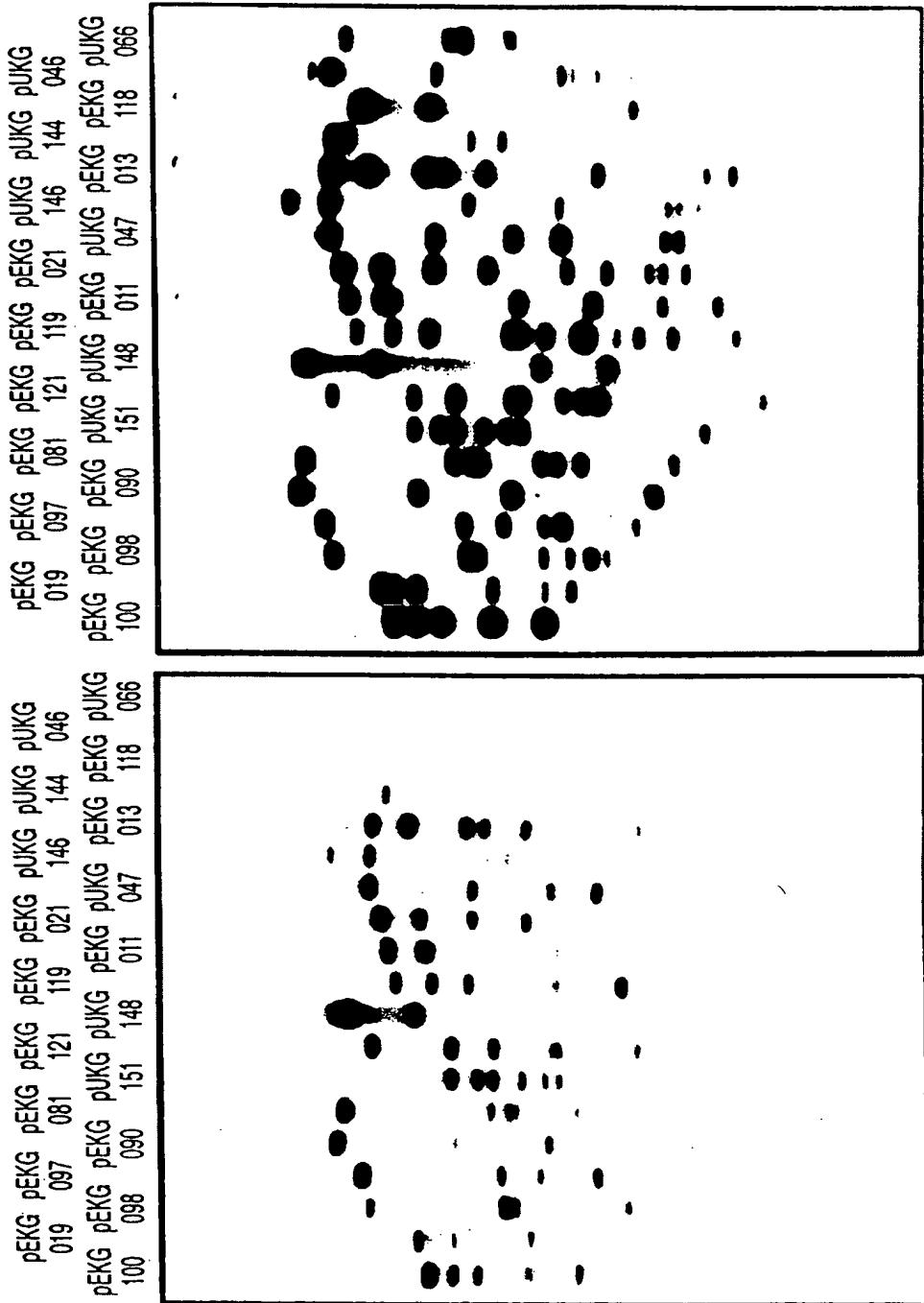


FIG. 17F

FIG. 17E



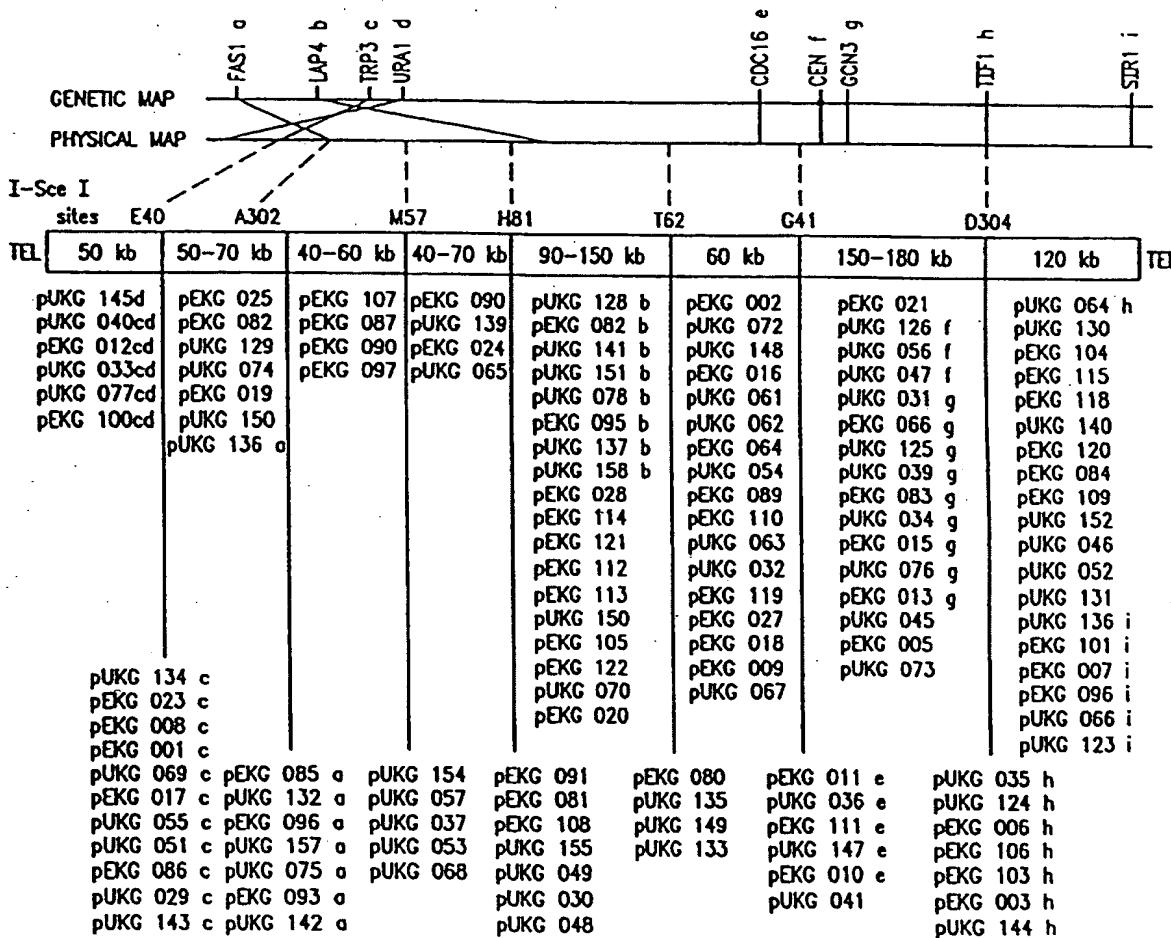


FIG. 18

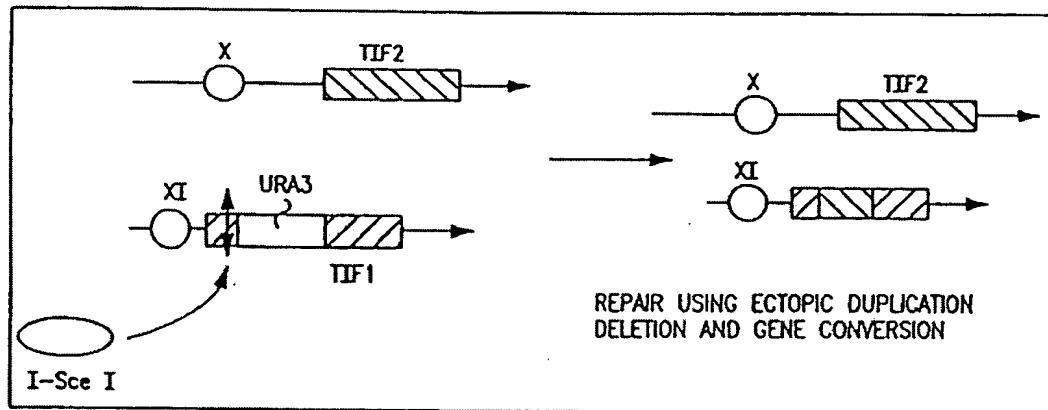


FIG. 19A

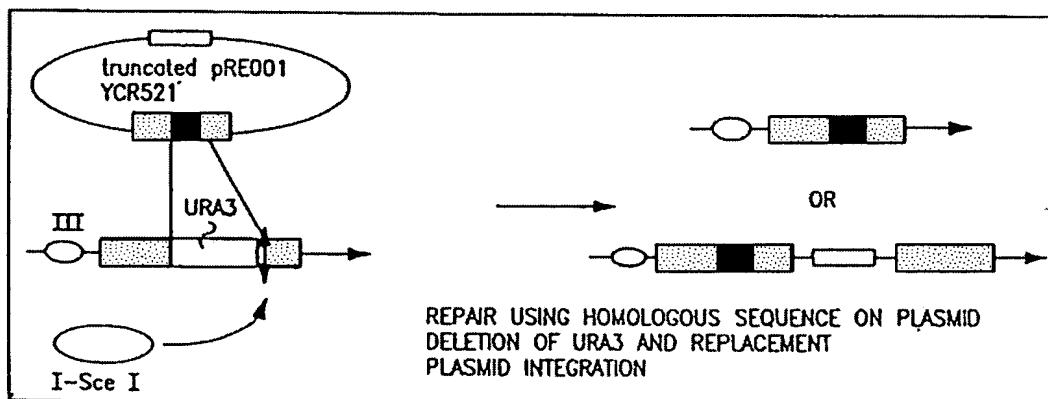
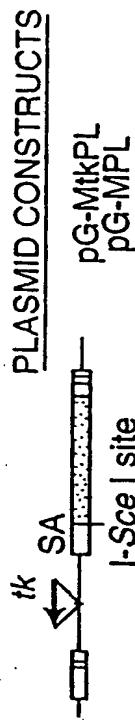


FIG. 19B

FIG. 20A



RETROVIRAL INFECTION

FIG. 20B

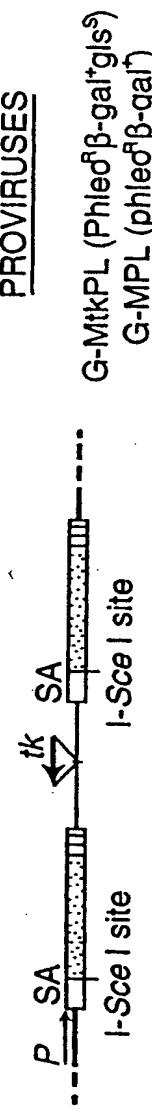


FIG. 20C

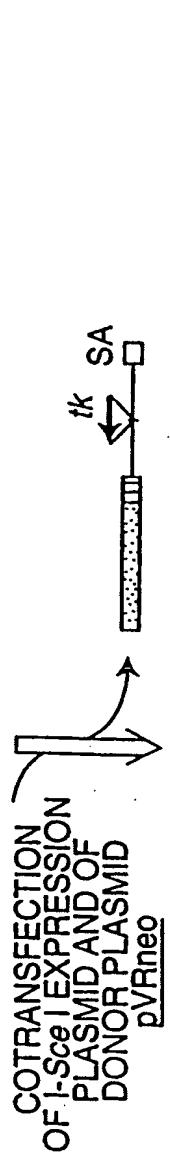
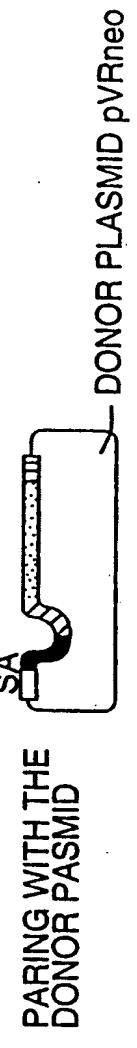
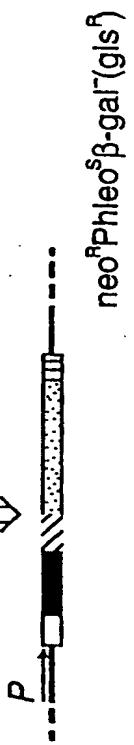


FIG. 20D



GENE REPLACEMENT

FIG. 20E



Legend

□ LTR ■ PhleoLacZ ■ NEO ▲ POLY A — GENOMIC DNA ← tk THYMIDINE KINASE

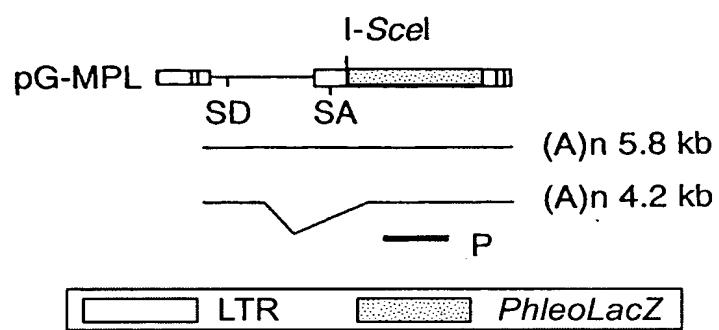


FIG. 21A

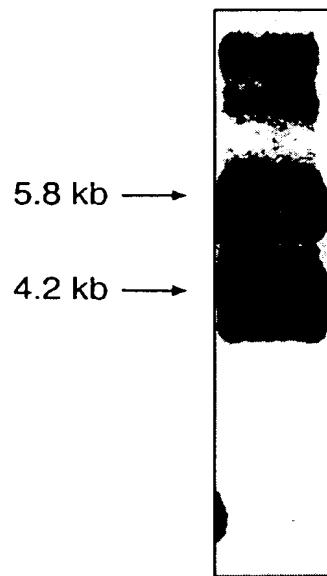
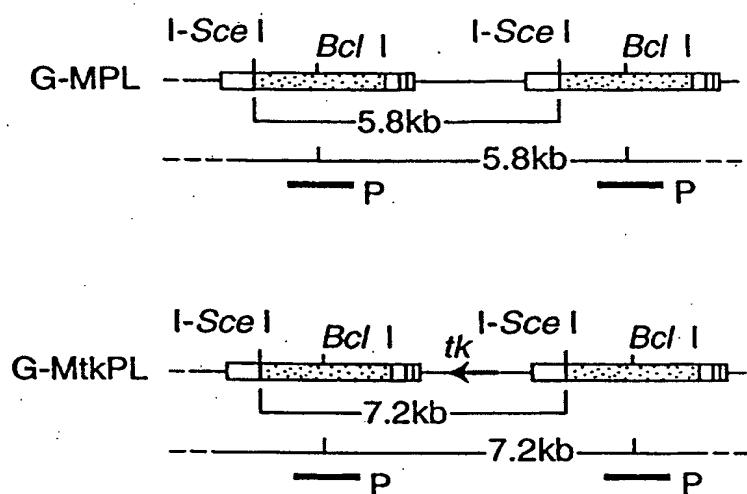


FIG. 21B



□ LTR PhleoLacZ ← tk THYMIDINE KINASE

FIG. 22A

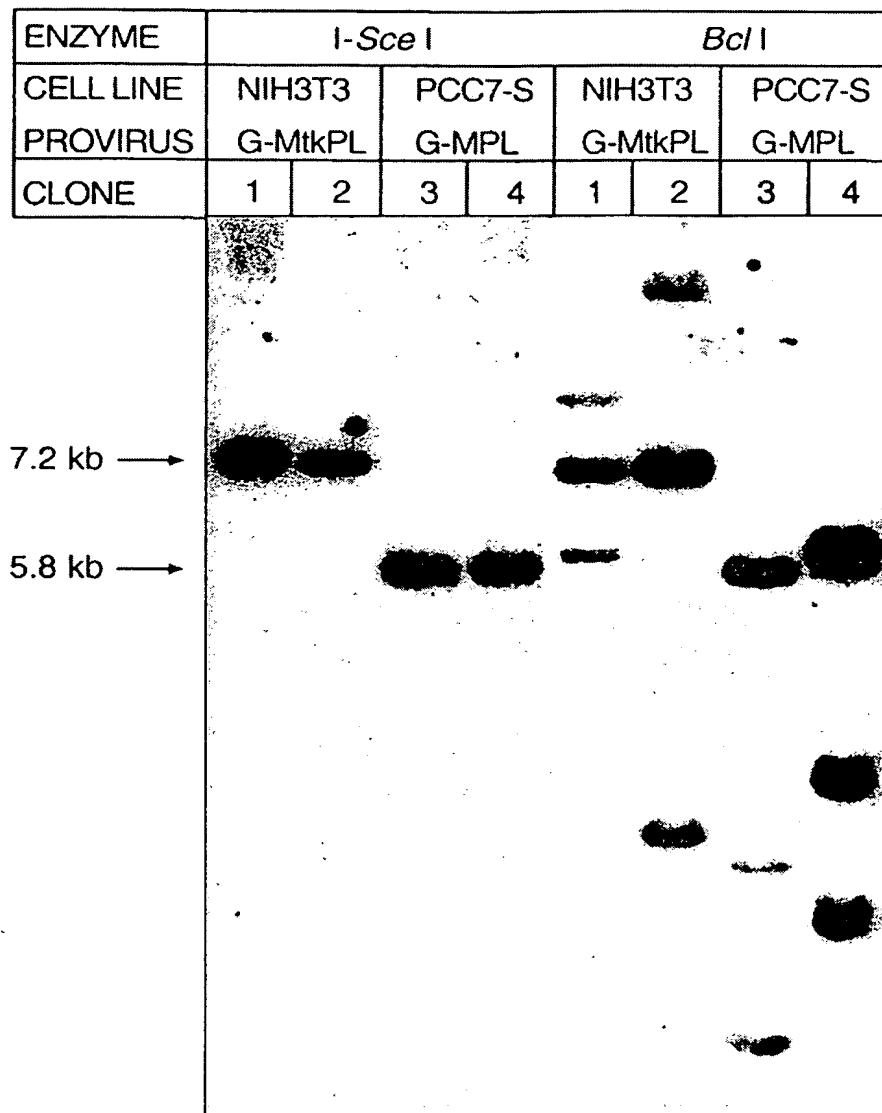
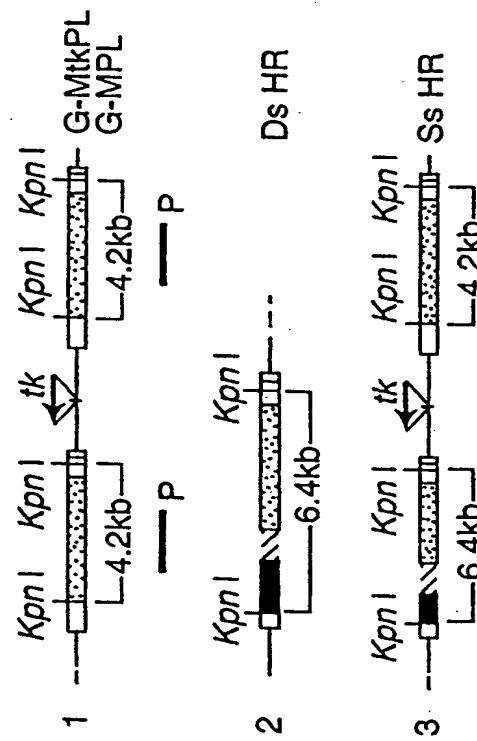


FIG. 22B



□ LTR ■ *PhleoLacZ* ■ *NEO* △ *POLY A* — GENOMIC DNA ← \downarrow *tk* THYMIDINE KINASE

FIG. 23A

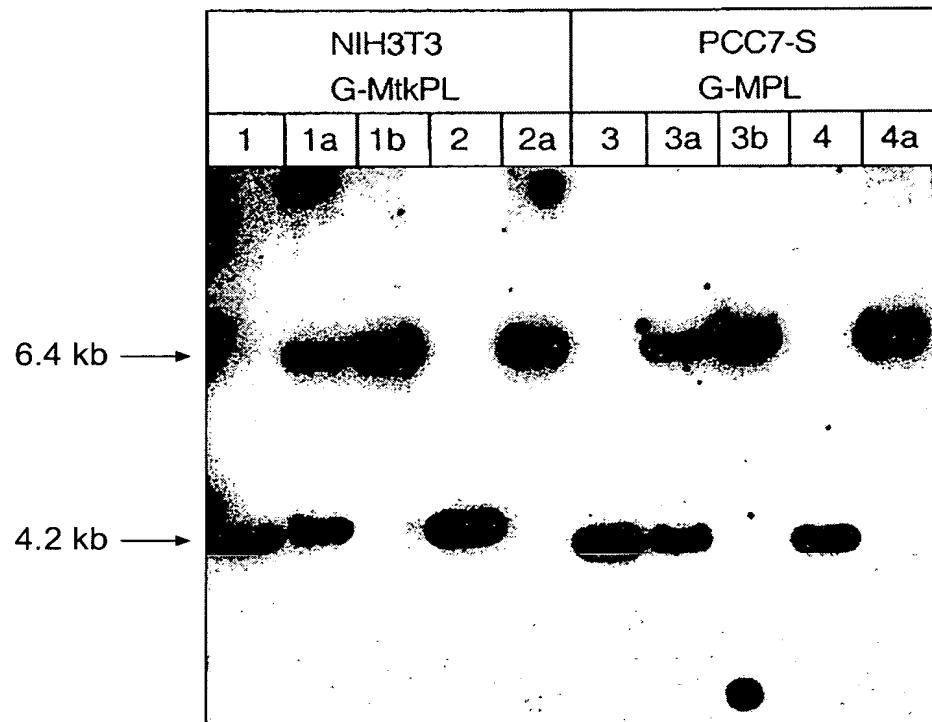


FIG. 23B

PCC7-S / G-MPL, CLONE 3

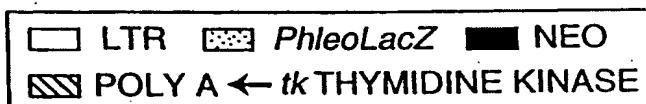
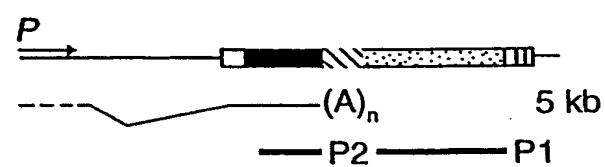
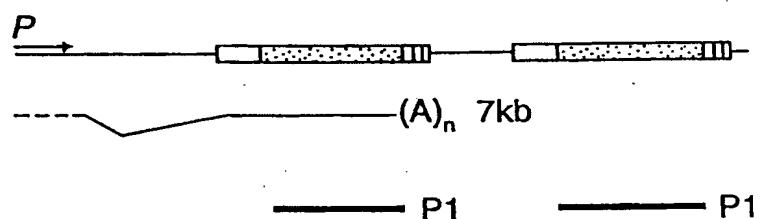


FIG. 24A

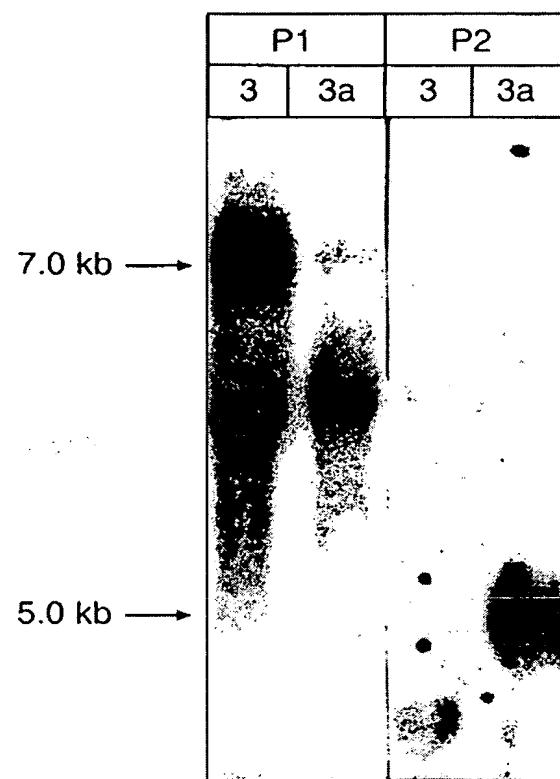
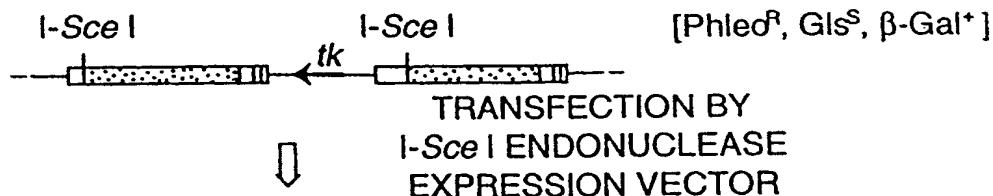


FIG. 24B

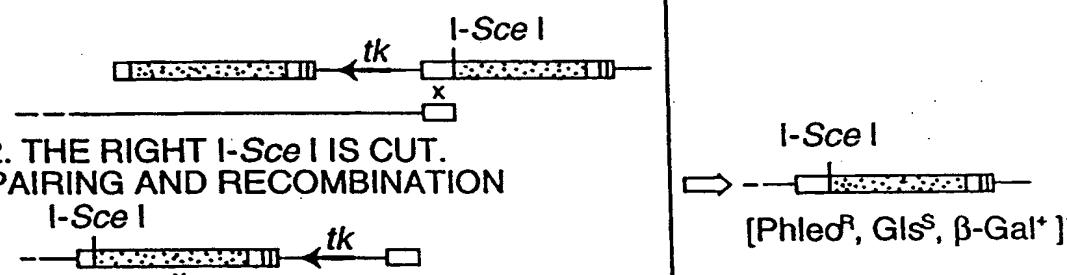
A. CHROMOSOMAL DNA CONTAINING PROVIRUS

PHENOTYPES



B. INTRA-CHROMOSOMAL RECOMBINATIONS EVENTS

1. THE LEFT I-SCE I IS CUT. PAIRING AND RECOMBINATION



3. BOTH I-SCe I SITES ARE CUT. RELIGATION BY END-JOINING

C. INTER-CHROMOSOMAL RECOMBINATION EVENT

BOTH I-Sce I SITES ARE CUT. GAP REPAIR USING INTACT CHROMOSOME SEQUENCES

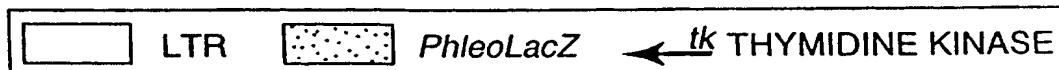
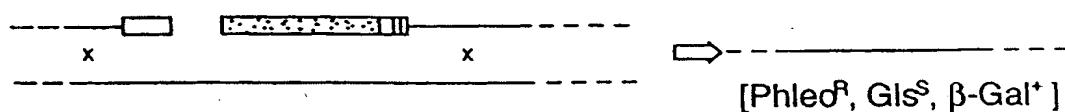


FIG. 25

A. PARENTAL DNA, G-MtkPL

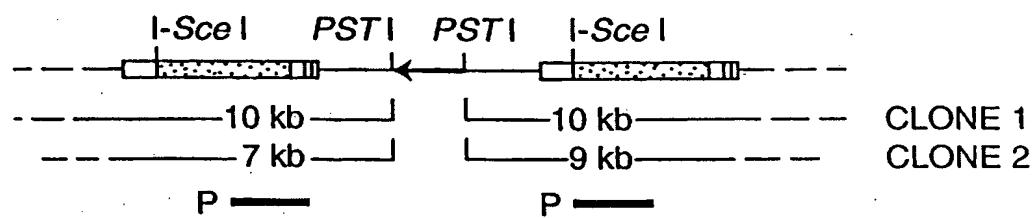


FIG. 26A

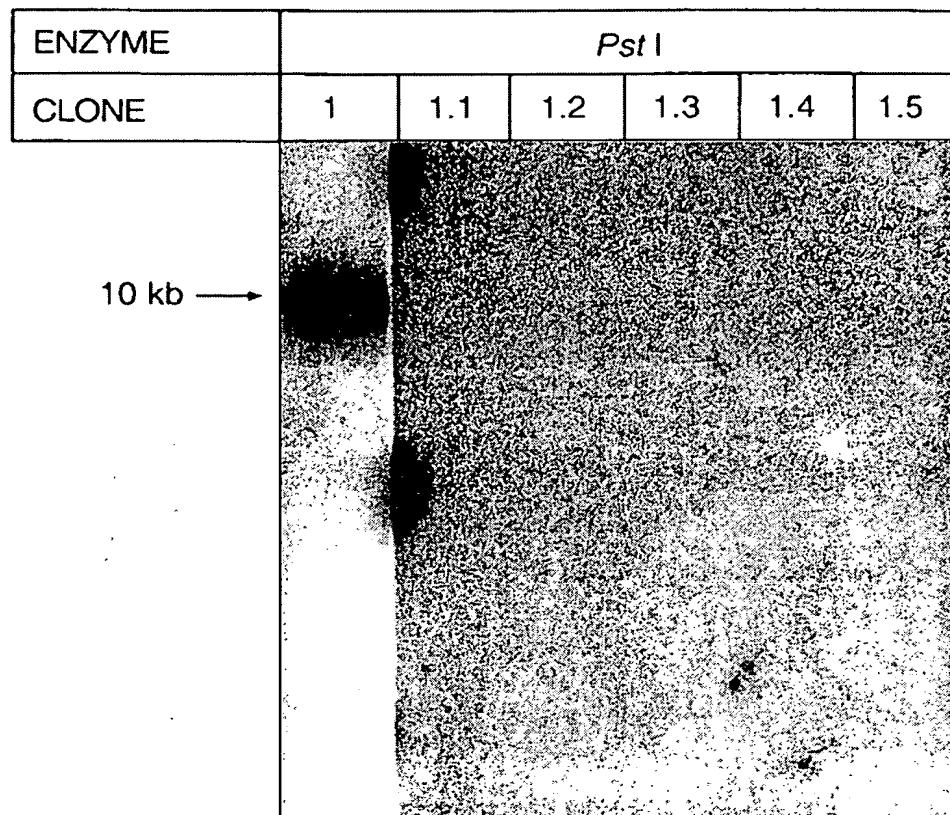


FIG. 26B

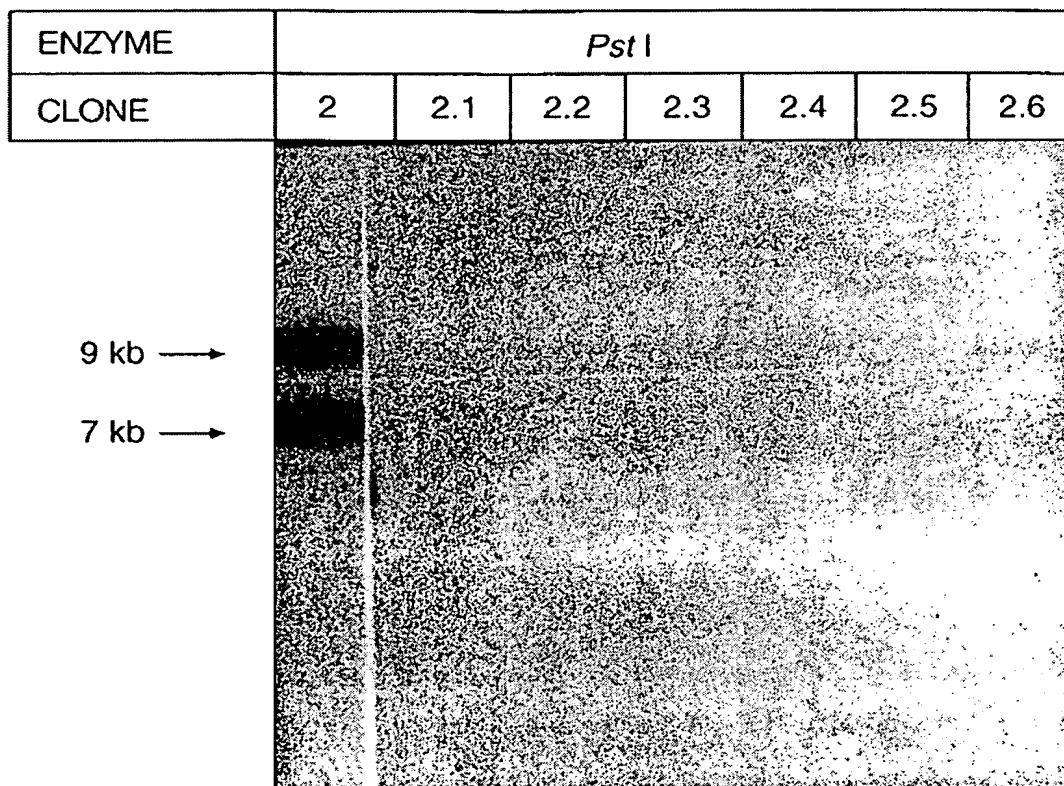
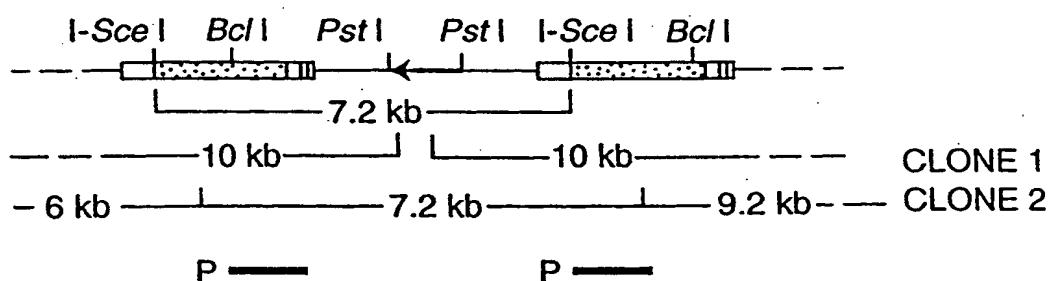


FIG. 26C

1. PARENTAL DNA, G-MtkPL



2. INTRA-MOLECULAR RECOMBINATION EVENT

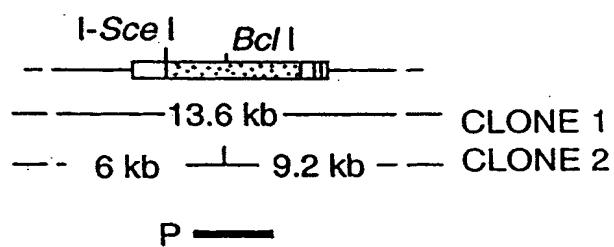


FIG. 27A

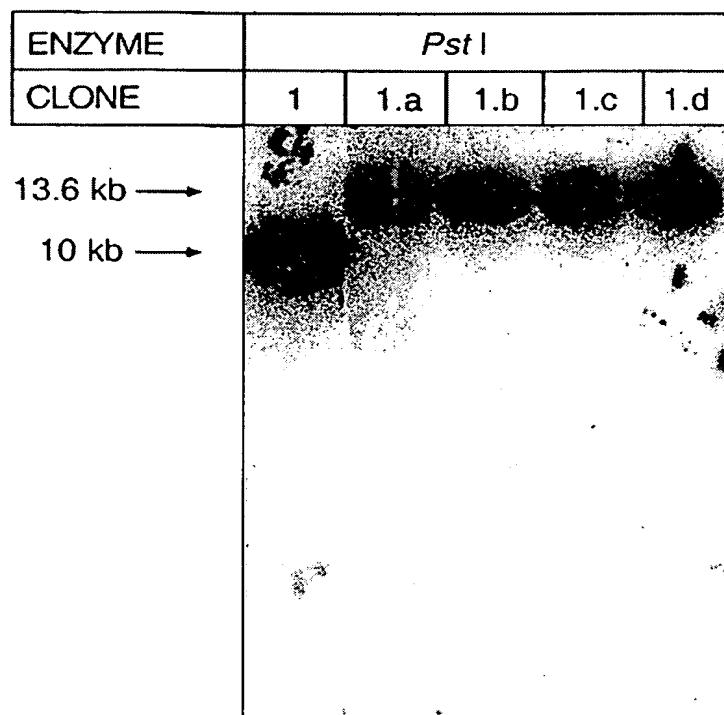


FIG. 27B

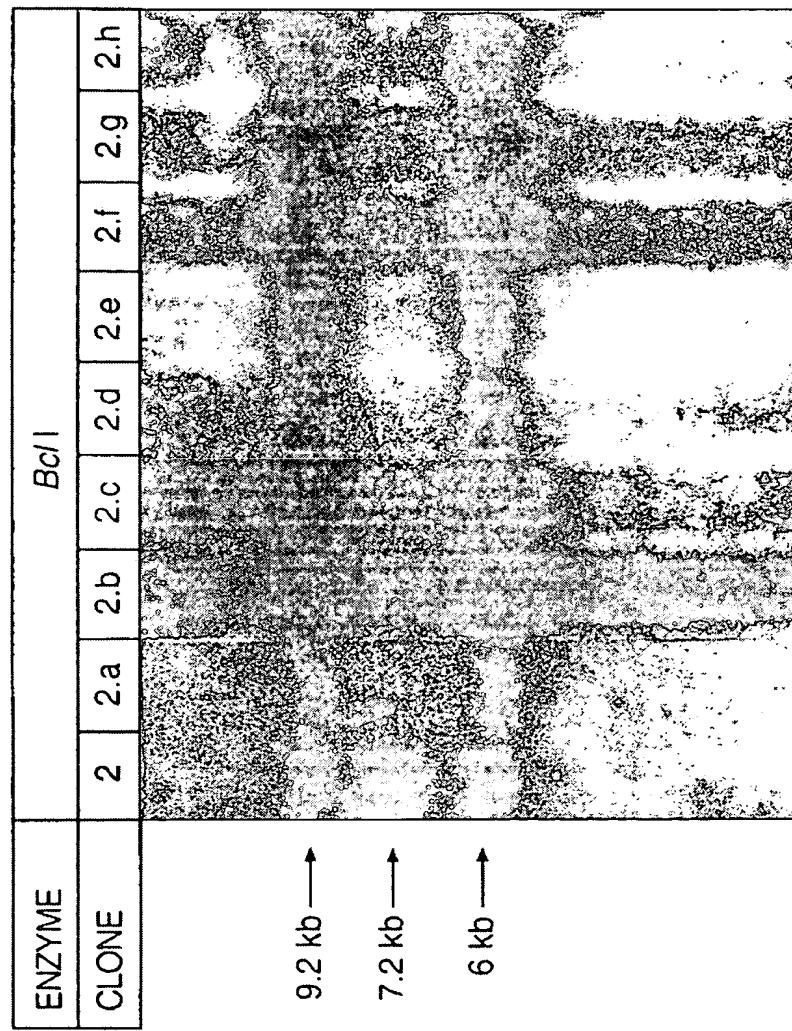
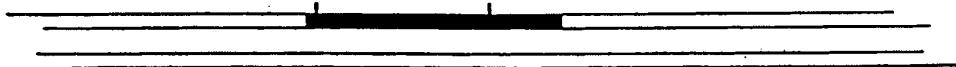


FIG. 27C

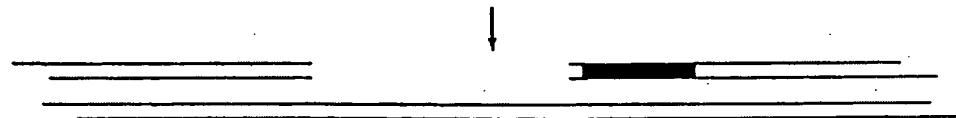
LOSS OF HETEROZYGOSITY

**INTEGRATION OF ARTIFICIAL SITE OR
PRESENCE OF SPECIFIC SITE**

I-Sce I



EXPRESSION OF I-Sce I AND SPECIFIC CLEAVAGE



REPAIR OF THE DSB WITH THE OTHER CHROMATID

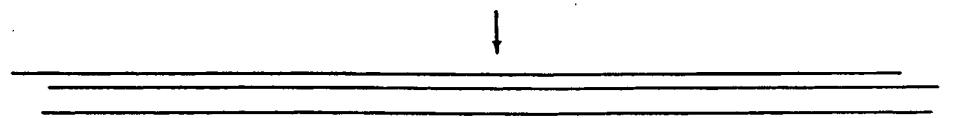


FIG. 28

CONDITIONAL ACTIVATION (TANDEM REPEAT)

INTEGRATION OF ARTIFICIAL SITE BETWEEN TANDEM REPEATS



EXPRESSION OF I-Sce I AND SPECIFIC CLEAVAGE



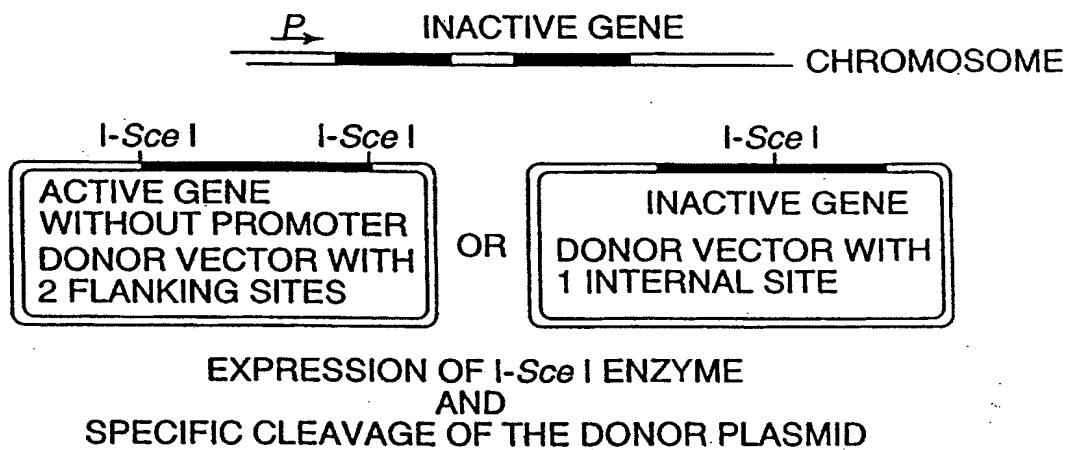
REPAIR OF THE DSB BY SINGLE STRAND ANNEALING



FIG. 29

ONE STEP REARRANGEMENT

INTEGRATION OF ARTIFICIAL SITE OR PRESENCE OF SPECIFIC SITE



RECOMBINATION BETWEEN THE CHROMOSOME AND PLASMID

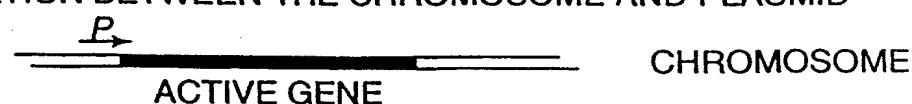
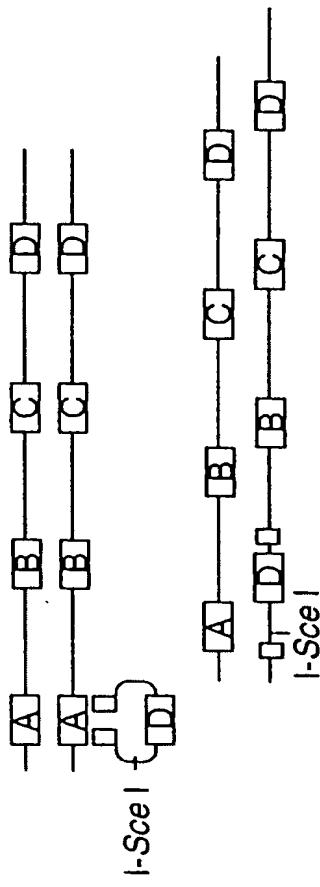


FIG. 30

DUPLICATION OF A LOCUS

1. INSERTION OF I-Sce I SITE BY CLASSICAL GENE REPLACEMENT



2. SPECIFIC CLEAVAGE BY I-Sce I ENZYME AND REPAIR OF THE BREAK BY HOMOLOGOUS SEQUENCES

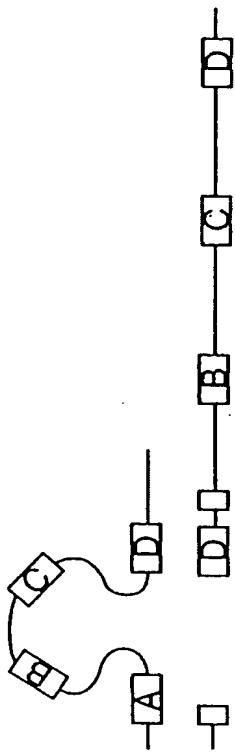
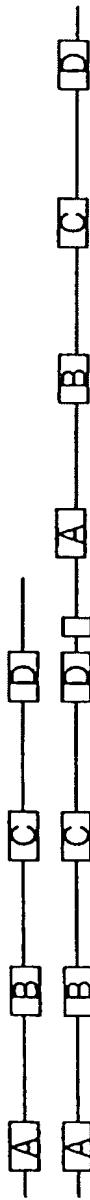


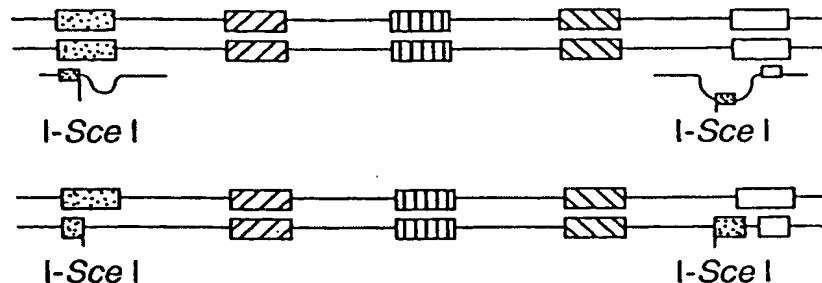
FIG. 3I

3. DUPLICATION OF THE TOTALITY OF THE LOCUS

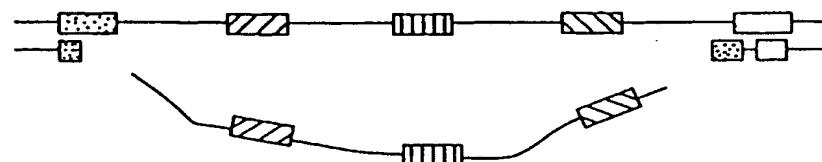


DELETION OF A LOCUS

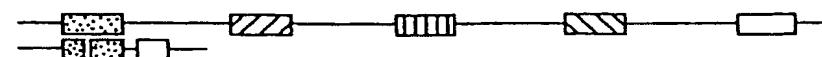
1 INSERTION OF TWO I-Sce I SITES FLANKING THE LOCUS



2 EXPRESSION OF THE ENZYME AND CLEAVAGE



3 RECOMBINATION BETWEEN THE TWO ENDS



4 DELETION OF THE LOCUS

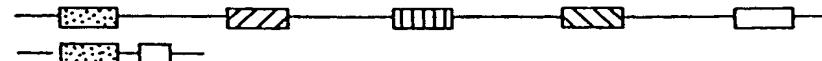


FIG. 32

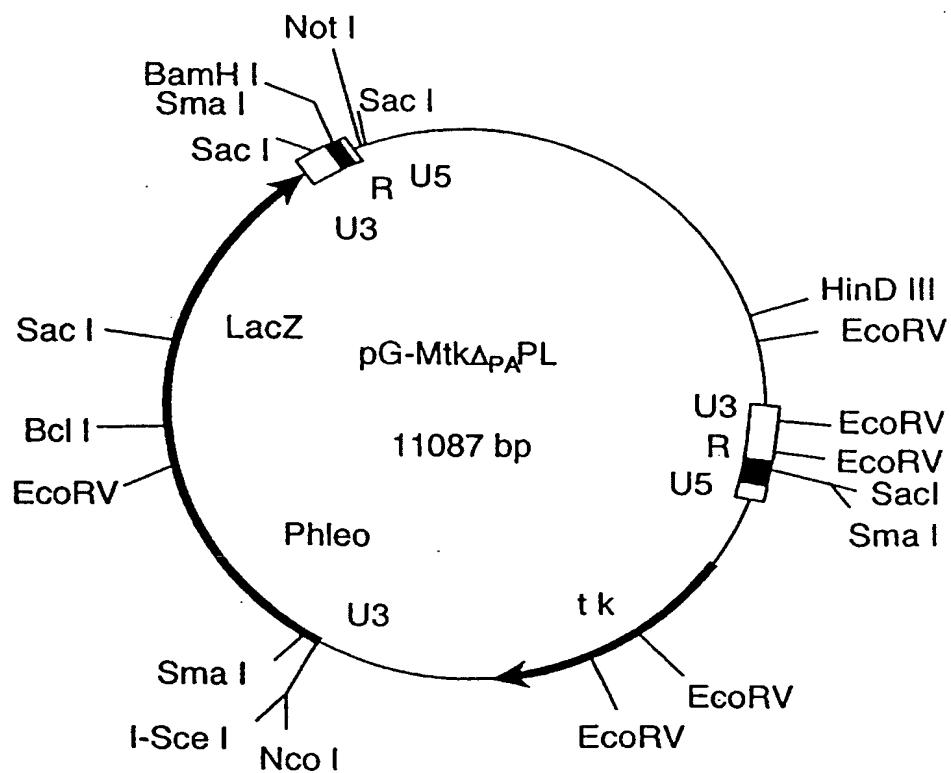


FIG. 33